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EPIDEMIOLOGY

Through the Looking Glass at Early-Life Exposures and Breast Cancer Risk

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The global increase in the proportion of women diagnosed with breast cancer, inadequate access to screening and high cost of treatment for breast cancer argue strongly for a greater focus on preventive strategies. But at what age is it appropriate to begin targeting preventive approaches? The recognized role of perinatal nutrition in neurologic development and the relation of maternal nutritional status to birthweight and subsequent risk of hypertension, diabetes, and cardiovascular disease identify pregnancy and early childhood as potential phases for prevention. This review examines indicators of hormonal and nutritional exposures in early life and breast cancer risk through the lens of the life course paradigm integrated with maternal and child health research and methodology. Compared to women who were normal birthweight (2500–3999 g), women who weighed ≥4,000 g at birth have a 20 percent to 5-fold increased risk of premenopausal breast cancer. Women born preterm and likely to be small- or large-for-date also have an increased risk. Birth length is directly associated with risk and has a larger magnitude of effect than birthweight. Prior preeclamptics and their daughters have a lower risk of breast cancer than comparable normotensives. An association between infant feeding practices and breast cancer is unclear without improved exposure assessment and analysis. Rapid childhood and pubertal linear growth increases breast cancer risk, while greater body fat over the same periods reduces risk. Growth data thus far have not been calculated in Z-scores from reference growth curves for comparison across studies. Events and secular trends influencing birth cohorts may not be adequately addressed, thereby limiting the interpretation and implications of the findings. Research in nonhuman primates may help uncover underlying mechanisms.

Keywords Breast cancer risk; Early-life exposures

INTRODUCTION

Several paradigms of the ''developmental origins of health and disease'' and the life course have appeared over the past decade.[1–4] The life history paradigm compares resource (i.e., energy and time) allocation across species during growth, reproduction, and maintenance.[1] The life course approach examines biological and psychosocial exposures over developmental and adult phases to assess cumulative risk of chronic disease.[2,5] The reverse-J shaped association of birthweight and coronary heart disease is an illustrative example of the ''developmental origins of disease'' paradigm.[6,7] These paradigms[1,5,8] share an intergenerational orientation and a similar approach of examining risk of intermediate endpoints or chronic disease from early-life exposures across developmental phases; however, few reviews[9,10] have addressed cancer as the endpoint. Moreover, the influence of early life on cancer has *not* been examined integrating findings from epidemiologic research in the fields of maternal and child health and of breast cancer. Therefore, the purpose of this article is to review the evidence for the relation of early-life exposures to breast cancer risk through the lens of the life course paradigm by: 1) describing hormonal and other factors that support a potential association of specific early-life exposures and breast cancer; 2) reviewing the magnitude of the estimate of effect of early-life exposures on cancer risk by developmental phase (i.e., in utero, infancy, childhood, and adolescence); 3) assessing methodologic issues and identifying areas for future research.

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TABLE 1a
Adjusted relative risk of breast cancer by study design, birth year, ethnic group, menopausal status, and birth weight

Author[ref]	Birth year	Ethnic group	Cases†	Birth weight (kg)						P trend	Comments
Cohort studies				<2.5	2.5–2.9	3.0–3.4	3.5–3.9	≥4.0			
McCormack[41]	1915–1929	¥	63[1]		1.0 (ref)	1.6	2.4*	3.5*		0.01	Birth Cancer Registry (B-ca registry), proxy indicators for adult risk
		¥	296[2]		1.0 (ref)	0.8	1.0	0.9		NS	
Dos Santos Silva[a][42]	1946	¥	21[0]		1.0 (ref)	1.4	2.2	5.0*		0.03	Adjusted for childhood a nd adult risk factors
		¥	59[3]		1.0 (ref)	1.0	1.4	1.6		NS	
				<2.0	2.0–2.9	≥3.0					Std Incidence Ratio reported; B-ca-registry, sampled neonates <35 wks gestation or <2,000 g and ≥35 wks gestation, no adjustment for adult risk factors; Standardized Incidence Ratios shown
Kaijser[43]	1925–1949	¥	19[1]	1.5	0.7	2.5					
		¥	39[3]	1.1	0.7	2.6*					
				2.5§	3.0	3.4	3.6	4.0			
Ahlgren[44]	1930–1975	¥	2074[3]	1.0 (ref)	1.0	1.1	1.1	1.2*		¶	Adjusted for childhood and adult risk factors
Case-control studies				<2.5	2.5–2.9	3.0–3.4	3.5–3.9	≥4.0	≥4.5		
Ekbom[n][45]	1874–1961	¥	1068[3]	0.8	1.0 (ref)	1.0	1.0	1.0		NS	B-ca registry, no adult risk factors; nested within a cohort
Titus-Ernstoff[46]	1911–1945	¥	1716[2]	1.1	0.9	1.0 (ref)	1.1	0.9	1.2	NS	Self-reported data after diagnosis; nested within a cohort
Michels[47]	1921–1965	¥	550[3]	0.6	0.7*	0.7*	0.9	1.0 (ref)		<0.01	Self reported after diagnosis; adjusted for adult risk factors; nested within a cohort
Lahmann[48]	1924–1950	¥	88[2]		1.0 (ref)	1.9	2.3	2.7		¶	Birth records; adjusted for adult risk factors; nested within a cohort

Sanderson[49]	1932–1973	#	288[3]	0.9	1.0 (ref)	1.1	0.8	0.7	NS	Maternal recall after diagnosis; adjusted for adult risk factors
Sanderson[51]	1944–1969	¥	746[3]	1.3	1.0 (ref)	1.3*	1.2	1.7*	0.06	Self reported after diagnosis; no adjustment for adult risk factors
	1924–1940	¥	401[3]	0.9	1.0 (ref)	1.1	0.8	0.6	0.06	
Sanderson[50]	1945–1947	¥	510[1]	1.2	1.0 (ref)	1.0	1.0	1.3	NS	Maternal recall after diagnosis; adjusted for adult risk factors
Mellemkjaer[52]	1935–1966	¥	881[1]	1.6	0.8	1.0 (ref)	1.0	1.3		B-ca-registry, no adult risk factors
				<3.1	3.1–3.4	3.5–3.7	>3.7			
Vatten[53]	1910–1970	¥	373[3]	1.0 (ref)	1.1	1.2	1.4*		0.02	B-ca-registry, adjusted for adult risk factors
Hodgson[54]	1949–1978	£	83[3]	1.1	1.0 (ref)	0.4			NS	Birth hospital record data
		¥	108[3]	0.9	1.0 (ref)	0.9			NS	
				<1.5	1.5–2.4	2.5–3.4	3.5–4.4	≥4.5		
Innes[55]	1958–1981	£, ¥	484[1]	3.0*	1.5*	1.0 (ref)	1.1	3.1*		B-ca-registry; no adjustment for adult risk factors
				1.16–2.94	2.95–3.34	3.341–4.45				
Le Marchand[56]	1946 on	#, ¥	71[1]	1.0 (ref)	0.7	0.8			NS	B-ca-registry; no adjustment for adult risk factors

£, African American.
¥, Non-Hispanic White.
#, Asian.
NS, nonsignificant.
[†]Menopausal status: [0]=premenopausal; [1]=premenopausal based on age <50 years; [2]=postmenopausal based on age ≥50 years; [3]=both.
*95% confidence interval excludes one.
[a]Includes cases from De Stavola[113]
[§]Median of each quintile.
[¶]Ahlgren[44] O.R. per kg increase 1.1 (95%C.I. 1.01–1.20); Lahmann[48] O.R. per 100 g increase 1.1 (95%C.I. 1.00–1.12).
[n]Includes cases from Ekbom (1992).

Methods: Search, Selection Criteria, and Strategy

Peer reviewed published studies in English were located using the *Medline* (National Library of Medicine, USA), *PubMed*, and references from original articles found in Pubmed and other search engines through November 1, 2004. Subject search terms included breast cancer risk or incidence and the following: ''in utero,'' fetal, preeclampsia, birthweight, birth length, preterm, breast or infant feeding, infancy, childhood, puberty, adolescence, (catch-up) growth, age at menarche, maternal and paternal age, birth order or parity, intergenerational, and programming. The review was restricted to research on singletons as opposed to multiple gestations. Epidemiologic and clinical research in the ''search'' areas were considered relevant if two or more terms were examined in the same analysis with an outcome of newborn's status, growth, age at menarche, or breast cancer. One individual (MRF) performed the original search with quality control checks on searches by one of the other coauthors. The strategy was to: 1) evaluate results in light of the design, sample size, adjustment for adult risk factors[11] and potential sources of bias; 2) synthesize the findings in tabular form; 3) evaluate whether information from child health research was taken into consideration in the analysis of early-life exposures and breast cancer; and 4) formulate recommendations for future research.

THE FETAL PERIOD: BIRTHWEIGHT

Rationale: A woman's lifetime hormonal exposure from endogenous metabolism and exogenous preparations is associated with breast cancer risk.[12,13] Hormonal exposure begins in utero when estrogen levels are as high as in puberty.[14] One indicator of intrauterine hormonal exposure is birthweight, which varies directly with: levels of maternal estrogen in pregnancy;[15–17] peak placental growth hormone at 37 weeks gestation;[18] and umbilical cord blood insulin growth factor-1 (IGF-1)[19–22] and leptin levels.[23] IGF-1 promotes postnatal somatic growth,[24] is a potent mitogen and anti-apoptotic agent in vivo,[25] and stimulates aromatization

TABLE 1b
Adjusted relative risk of breast cancer by study design, birth year, ethnic group, menopausal status, and birth length

Author[ref]	Birth year	Ethnic group	Cases†	Birth length (cm)					P trend	Comments
Cohort study										
				≤49.0	49.5–50.0	50.5–51.0	51.5–52.0	≥52.5		
McCormack[41]	1915–1929	¥	65[1]	1.0 (ref)	2.1	2.9*	3.5*	3.4*	0.001	Birth Cancer
		¥	294[2]	1.0 (ref)	1.0	1.1	0.8	1.3	NS	Registry (B-ca registry), proxy indicators for adult risk
Case control studies										
				<50.0	50.0	51.0	≥51.5			
Vatten[53]	1910–1970	¥	373[3]	1.0 (ref)	1.2	1.5*	1.3		0.02	B-ca-registry, adjusted for adult risk factors
				Quartile 1	Quartile 2	Quartile 3	Quartile 4			
Ekbom[n][45]	1874–1961	¥	1068[3]	1.0 (ref)	1.1	1.2	1.1		NS	B-ca registry, no adult risk factors; nested within a cohort

£, African American.
¥, Non-Hispanic White.
#, Asian.
NS, nonsignificant.
†Menopausal status: [0]=premenopausal; [1]=premenopausal based on age <50 years; [2]=postmenopausal based on age ≥50 years; [3]=both.
*95% confidence interval excludes one.
[n]Includes cases from Ekbom (1992).

of estrone to the more biologically active estradiol in breast cancer cells in vitro.[26] Adult IGF-1 levels are positively associated with breast cancer risk in premenopausal women.[27] Leptin increases breast cancer cell growth in vitro.[28] Body mass index (BMI) varies directly with serum leptin concentrations and is positively associated with risk of postmenopausal breast cancer.[29]

Birthweight reflects intrauterine nutritional exposures and correlates directly with maternal weight gain in pregnancy,[30,31] parental birthweight,[32] and maternal prepregnancy BMI.[33,34] An estimated 40 percent of the variance in birthweight can be explained by genetic contributions[35,36] or by a form of trangenerational epigenetic inheritance.[37] The proportion of macrosomic ($\geq$4,000 g) newborns peaked in the United States in the 1980s at 11 percent and declined to 9.2 percent in 2002; this percentage varies by ethnic group.[38] African American and non-Hispanic White women from families where previous generations delivered neonates of low or high birthweight have a 2-fold increased risk of delivering a low or high birthweight neonate, respectively.[39,40]

Birthweight–Breast Cancer Association: Table 1a presents risk estimates from 4 cohort studies[41–44] and 12 case-control studies,[45–56] three of which were nested within cohort studies.[45,47,48] Compared to normal birthweight neonates (2.5–2.99 g), the high birthweight ($\geq$4,000 g) experienced a 20 percent to 5-fold increased risk of *premenopausal* breast cancer, except for a study in young women where a U-shaped relation of birthweight and breast cancer was observed.[55] In studies analyzing *pre-* and *postmenopausal* women in the same model, 4 of 10 have reported significantly increased risk in the category with the highest birth weight[44,51,53] or reduced risk in those weighing <4,000 g at birth compared to those weighing $\geq$4,000 g.[47] Research on birthweight and *postmenopausal* breast cancer also is inconsistent. Therefore,

TABLE 2
Adjusted relative risk of breast cancer by study design, birth year, ethnic group, and preterm birth

Author[ref]	Birth year	Ethnic group	Cases†	Gestational age (weeks)	R.R.	Comments
Birth-cancer registry studies						
Ekbom[45]	1874–1961	¥	10^3	<33	4.0*	Referent: $\geq$33 weeks
Le Marchand[56]	1946 on	#, ¥	9^0	<36	1.2	Referent: 36–40 weeks
Vatten[59]	1910–1970	¥	77^3	<32	1.2	Referent: $\geq$40 weeks,
		¥	291^3	32–36	1.1	P for trend=0.02
Mc Cormack[41]	1915	¥	63^1	30–38	2.1*	Referent $\geq$41 weeks; P for trend=0.03
					Std. incidence ratio	
Kaijser[43]	1925–1949	¥	19^1	$\leq$32	1.4	Referent: birth weight <2,000 g and gestation >35 weeks
				33–34	0.9	
		¥	39^3	$\leq$32	1.1	
				33–34	0.9	
Ekbom[60]	1925–1934	¥	12^3	<31	6.7*	Referent: birth weight <2,000 g and gestation >35 weeks
				31–32	2.3	
				33–34	0.7	
				$\geq$35	0.2	
Case-control studies						
					R.R.	
Michels[47]	1921–1965	¥	8^3	Preterm	1.0	Referent: not preterm
Sanderson[50]	1945–1947	¥	18^1	<37	0.9	Referent: 37–42 weeks; crude O.R. provided

¥, Non-Hispanic White.

#, Asian.

†Menopausal status: ^{0}=premenopausal; ^{1}=premenopausal based on age <50 years; ^{2}=postmenopausal based on age $\geq$50 years; ^{3}=both.

*95% confidence interval excludes one.

the literature is most suggestive of an association of high birthweight neonates and risk of *premenopausal* breast cancer after adjustment for adult risk factors (in the comments to Table 1a). Of note, the research largely has been conducted in non-Hispanic White women. Two studies in Asians[49,56] report no association between birthweight and breast cancer. Asians have a more peaked birthweight distribution and a smaller proportion of low and high birthweight neonates than Caucasians[57] to detect an association in the extremes of the distribution.

Three linked birth-cancer registry studies examine the relation of birth length and breast cancer risk[41,45,53] (Table 1b). All three studies demonstrate a positive trend of higher breast cancer risk in *premenopausal* or *pre-* and *postmenopausal* patients who were 51 cm or more in length at birth. Two report significant trends after adjustment for gestational age and adult risk factors. The risk is larger than the risk for birthweight alone, indicating that growth factors specific to linear bone growth may play an important role in breast cancer etiology.[41,53]

THE FETAL PERIOD: PRETERM BIRTHS

Rationale: Women who deliver preterm have higher estradiol levels than those who deliver full term.[17] Preterm neonates (<37 weeks gestation) have higher levels of gonadotropins than full-term neonates in early infancy. Gonadotropins stimulate the ovary to produce excessive amounts of estradiol, which are associated with an increased risk of ovarian cysts in adolescence; and since estrogens may have a direct mutagenic potential,[58] exposure to higher levels of estrogens in early postnatal life may lead to an increased risk of breast cancer.

Preterm Birth–Breast Cancer Association: Using linked birth-cancer registry data, the pattern of an increased risk of breast cancer for those born earlier appears in a significant trend of increasing risk (SIR) of breast cancer with decreasing gestation age of the neonate in three studies[43,59,60] and a significantly higher risk of breast cancer in newborns of gestation ages <33 weeks or 30–38 weeks.[41,45] In contrast, no association is observed in the case-control studies[47,50] (Table 2). Several caveats should be noted: 1) the cut-off for preterm births and, therefore, the referent group varies by study; 2) research is based on small numbers; and 3) women who deliver early may incorrectly recall gestational age of the index child because they never reached the landmark ''due date.''[61] Misclassification of preterm births based on maternal-reported gestational age might attenuate the relation of preterm births to breast cancer. Of note, in birth cohorts before the 1980s, neonatal intensive care units were not in existence to support survival of the preterm; therefore, survivors might be large-for-gestational age (LGA: $\geq$90th percentile of birthweight for newborns delivered each week of gestation) babies who had a high growth rate in utero (during a short pregnancy). Factors that stimulated intrauterine growth and a higher rate of mitotic division in the LGA neonate might have eventually led to an increased risk of breast cancer.[14]

THE FETAL PERIOD: MATERNAL AGE AND PREECLAMPSIA

Rationale: Maternal age-specific hormone levels in pregnancy have not been examined extensively. Pregnancy estriol levels do not vary by maternal age in one study,[16] but total estrogen (TE) and estradiol (E_2) levels are highest in women aged 20–24 years, lowest in teenagers, and intermediate in women aged 25 years and over in another study.[62] Maternal age covaries with parity, which exhibits a consistent hormonal pattern across three studies. Specifically, TE and E_2 levels (at 16 and 27 weeks gestation in one study, or at 26 and 31 weeks gestation in another study) are higher among women in their first than those in their second full-term pregnancy and higher in the same woman in her first than in her second pregnancy.[17,63] Maternal age is associated with risk of poor pregnancy outcomes. Compared to women aged 20–24 years, women aged 35 and older are at increased risk of delivering a newborn with birth defects, a marker of chromosomal aberrations and, in turn, cancer risk.[64] Compared to primiparous women aged 20–24 years, primiparous women aged 30 and older are at increased risk of delivering low birthweight neonates.[65] Compared to women aged 20–24 years, teenagers have fewer pregnancies and higher rates of small-for-gestational age (SGA: <10th percentile of birthweight for newborns delivered each week of gestation) and preterm births, thus, women aged 20–24 years are considered the referent group in maternal and child health research. In sum, if maternal age at the birth of the index case is related to breast cancer risk in the offspring, then the association may be via parity (and hormone levels), birthweight, and/or adverse pregnancy outcomes.

Maternal Age–Breast Cancer Association: Because the maternal age–breast cancer association has breast cancer rates of offspring of teenage mothers as the referent group, the relative risks (R.R.) are recalculated using cancer rates of daughters of women aged 20–24 years as the referent group (for the reasons mentioned above; Table 3). Data are presented from 10 case-control studies,[46,51,52,55,56,66–70] one of which, is a birth-cancer registry study and 2 are cohort studies.[71,72] The R.R. of breast cancer increases with increasing maternal age to 35–39 years in 5 studies and is slightly higher in offspring of teenagers in 4. The R.R. for the maternal age–breast cancer association remains the same after stratification by reproductive risk factors in the patient,[68,69,71] while a J-shaped relation was observed after adjustment for her birthweight.[55] Thus, maternal age is probably not a marker for hormonal exposures in utero, because the R.R. of breast cancer in offspring of the 20–24 year olds, who reportedly have the highest hormone levels in pregnancy, are not higher than those in offspring of other mothers.

TABLE 3
Revised relative risk of breast cancer by maternal age at birth of the index case, stratified by study design, year of study, ethnic group, and number of cases

Author[ref]	Birth year	Ethnic group	No. of cases†	Maternal age by year‡						Comments
Cohort studies				<20	20–24	25–29	30–34	35–39	40+	
Colditz[71]	1921–1946	¥	1799[3]	1.0	1.0 (ref)	1.1	1.1	1.1	1.0	P for trend NS
					<25	25–29	30–35	>35		
Zhang[72]	1886–1919	¥	149[3]		1.0 (ref)	1.2	1.3	1.1		
Case-control studies										
				<20	20–24	25–29	30–34	35–39	40+	
Rothman[66]	NR	£, ¥, #	4339[3]	0.9	1.0 (ref)	1.2	1.1	1.2	1.1	
Thompson[67]	1926–1962	£, ¥,	2492[3]-parous	1.1	1.0 (ref)	1.2	1.2	1.5*	1.3	
		£, ¥	499[3]-nulliparous	1.3	1.0 (ref)	1.1	1.2	1.6	0.7	
Janerich[68]	1875–1947	¥	2414[3]	1.0	1.0 (ref)	1.1	1.1	1.0	1.0	
Newcomb[69]	1913 on	¥	1253[3]	1.2	1.0 (ref)	1.2	1.1	1.4	1.1	Subject report after diagnosis; P for trend NS
Sanderson[51]	1944–1969	¥	746[3]		1.0 (ref)	1.0	1.2	1.0		
Mellemkjaer[52]	1935–1966	¥	881[1]		1.0 (ref)	1.1	1.1			B-ca-registry; P for trend NS
Titus-Ernstoff[46]	1911–1945	¥	1555[2]	1.0	1.0 (ref)	1.0	1.2	1.2	1.3	P for trend=0.04
Innes[55]	1958–1981	£, ¥	484[1]	1.2	1.0 (ref)	1.4*	1.5*	2.0*		P for trend=0.01
Weiss[70]	1948 on	£, ¥	2106[3]	1.0	1.0 (ref)	1.0	1.0	1.0		P for trend NS
				15–22	23–26	27–30	31–46			
Le Marchand[56]	1946 on	#, ¥	153[1]	1.2	1.0 (ref)	1.2	1.7			

£, African American.
¥, Non-Hispanic White.
#, Asian.
NR, not reported; NS, nonsignificant.
†Menopausal status: [0]=premenopausal; [1]=premenopausal based on age <50 years; [2]=postmenopausal based on age ≥50 years; [3]=both.
‡When a column is left blank the reader assumes that the O.R. includes all age categories older or younger.
*95% confidence interval excludes one.

Rationale for Preeclampsia: Preeclampsia, a condition characterized by pregnancy-induced hypertension, edema, and proteinuria, is diagnosed in 2 to 10 percent of pregnant women. Preeclampsia, known as the ''disease of theories,'' may be more than one disease of heterogeneous origin with early and late onset patients who vary by severity of disease[73–75] and who deliver neonates at risk of SGA or LGA.[76,77] Increased cardiac output of late-onset preeclamptics may enhance uteroplacental profusion, which increases the risk of delivering LGA neonates, while severe, early-onset patients may experience reduced uteroplacental profusion, which increases the risk of delivering SGA.[76] Levels of dehydroepiandosterone sulfate (DHEAS) in the cord blood of neonates are highest in severe hypertensives in pregnancy, intermediate in the moderate hypertensives, and lowest in mild hypertensives who have comparable levels to neonates of normotensive women.[78,79] Within strata of birthweight-for-gestational age, cord blood levels of IGF-1 are lower, but levels of IGFBP-1 and leptin are higher in offspring of severe preeclamptics than in normotensive controls.[80,81] Estrogen and androgen concentrations do not differ in cord blood of preeclamptic compared to normotensive offspring in another study.[82]

Preeclampsia Exposure in utero and Breast Cancer Risk: In several studies, daughters of preeclamptics have a 10 to 60 percent lower risk of breast cancer than daughters of normotensives[45,50,55] (Table 4).

Although, so far, breast cancer risk in offspring of preeclamptics has been discussed, preeclampsia also influences the risk of breast cancer in the mothers. Compared to normotensive pregnant women, preeclamptics have higher levels of progesterone, of androgen precursors of estrogen

TABLE 4
Adjusted relative risk of breast cancer in the mother or daughter by maternal preeclampsia (yes vs. no), birth year, and ethnic group

Author[ref]	Birth year	Ethnic group	No. of cases‡/ total no. cases†	Criteria of diagnosis	R.R.	Comments
Daughter's risk						
Ekbom[45]	1874–1961	¥	14/1068[3]	Toxemia	0.4*	B-ca-registry; no adult risk factors
Sanderson[50]	1944–1947	¥	20/509[3]	Preeclampsia or eclampsia	0.8	Maternal recall, adjusted for adult risk factors
Innes[55]	1957–1981	£, ¥	6/462[1]	Toxemia	0.9	B-ca-registry; no adult risk factors
Maternal risk						
Polednak[86]	1926 on	¥	2/314[1]	Toxemia	0.3*	Case-control; hospital record data
Thompson[87]	1926–1962	£, ¥	139/3,897[3]	Hypertension	0.7*	Diagnosed with hypertension before the end of the most recent term pregnancy; case recall
Troisi[88]	1946–1972	£, ¥	97/1,236[3]	Toxemia	0.8	Case-control; case recall
Vatten[89]	NR	¥	280/5,474[3]	Preeclampsia or hypertension	0.8*	B-ca-registry; analysis restricted to primiparous women
Innes[90]	NR	£, ¥, §	95/2,404[3]	Preeclampsia	0.9	B-ca-registry, case-control; analysis restricted to primiparous women
					Delivery	
					Preterm / Term	
				Normotensive	1.0 / 1.0	NS
				Preeclampsia or hypertension	0.9 / 0.8*	
					R.R.	
Paltiel[91]	NR	€	40/91[3]	Preeclampsia	1.4*	Cohort of births 1964–1976; linked to cancer registry

£, African American.
¥, Non-Hispanic White.
§, Hispanic.
€, Includes Israel, West Asia, and North Africa.
NR, not reported; NS, nonsignificant.
‡Number of breast cancer cases diagnosed with toxemia, preeclampsia, or hypertension in pregnancy.
†Menopausal status: [0]=premenopausal; [1]=premenopausal based on age <50 years; [2]=postmenopausal based on age ≥50 years; [3]=both.
*95% confidence interval excludes one.

(e.g., DHEAS), cortisol, insulin, and human chorionic and other gonadotropins in pregnancy, but lower levels of estrogen and of IGF-1.[78,79,83,84] Twenty-two women with prior preeclampsia and a similar number of normotensive control women, matched on age and BMI, were studied on average 17 years postpartum.[85] Compared to the normotensives, women with a history of preeclampsia had elevated levels of free testosterone, free androgen, and free testosterone to estradiol ratios in serum.

Preeclampsia—Maternal Breast Cancer Association: Women who report a diagnosis of preeclampsia (eclampsia, toxemia, or pregnancy-induced hypertension) have a 10 to 70

percent lower risk of breast cancer,[86–90] except in one cohort study[91] that describes a 40 percent higher risk in prior preeclamptics (Table 4). All but the cohort study of Middle Eastern women in Jerusalem, Israel by Paltiel[91] are conducted in European/non-Hispanic White populations. R.R.s vary by criteria for diagnosis and by parity, as illustrated by the R.R. of 0.3 in nulliparous preeclamptic women;[86] the R.R. of 0.7 in all women diagnosed with pregnancy-induced hypertension in contrast with a R.R. of 1.1 in nulliparous women in the same study.[87] Thus, the criteria for diagnosis of preeclampsia may alter the magnitude of breast cancer risk; while underlying disease etiology as yet unknown may be protective or conducive to breast cancer. Potential mechanisms underlying the lower risk of breast cancer in preeclamptics include: the index pregnancy may lower estrogen and/or IGF-1 levels postpartum and in turn lower breast cancer risk; or complex mechanisms related to programming from life-long androgenic exposures and genetic variants associated with preeclampsia may influence breast cancer risk.

INFANCY: BREAST AND BOTTLE FEEDING

Rationale: Human breast milk and infant formula from cow's milk or soy are the major sources of nutrition in infancy. Breast milk composition reflects maternal diet, nutritional status, hormone levels, and environmental exposures. Hormones such as IGF-1 in breast milk vary in concentration by age of the infant as well as by phase of the menstrual cycle in the mother.[92] The major hypothesis relating breast milk intake to breast cancer risk arises from the animal work of Bittner in the 1930s wherein a factor (later identified as a retrovirus) present in mouse milk was essential for the

TABLE 5
Adjusted relative risk of breast cancer by study design, birth year, if breastfed (bottle fed), and duration of breastfeeding

Author[ref]	Birth year	Ethnic group	% Breast feeding: Cases†	% Breast feeding: Controls		R.R.	Comments
Cohort studies							
Michels[107]	1921–1964	¥	36.3^{0}		Ever	1.0§	Referent: never breastfed
					Duration	R.R.	
					≤3	0.7§	Referent: never breastfed;
					4–8	1.0§	adjusted for multiple
					≥9	0.9§	covariates; P for trend NS
		¥	73.5^{2}		Ever	1.1	Referent: never breastfed
					Duration	R.R.	
					≤3	1.3§	Referent: never breastfed;
					4–8	0.9§	adjusted for multiple
					≥9	1.3§	covariates; P for trend NS
Case-control studies							
Brinton[104]	NR	¥	73.7^{3}	74.3	Ever	0.9§	Referent: never breastfed
Ekbom[105]	1874–1954	¥	88.9^{3}	88.1	Ever	1.0	Referent: never breastfed
Freudenheim[103]	1901–1951	¥	48.9^{0}	58.5	Ever	0.7	Referent: never breastfed;
			80.6^{2}	85.7	Ever	0.7	adjusted for age and education
Weiss[70]	1936–1972	¥	41.7^{1}	49.5	Ever	0.7§	Referent: never breastfed
Titus-Ernstoff[106]	1942–1945	¥	42.0^{0}	48.1	Ever	0.7	Referent: never breastfed
			55.6^{2}	55.8	Ever	1.0	
Sanderson[61]	1944 on	¥	44.5^{1}	44.6	Ever	1.0	Referent: never breastfed
					Duration	R.R	
					<3	1.0	Referent: never breastfed
					3–5.9	1.1	
					≥6	1.0	

£, African American.
¥, Non-Hispanic White.
#, Asian.
NR, not reported; NS, nonsignificant.
†Menopausal status: ^{0}=premenopausal; ^{1}=premenopausal based on age <50 years; ^{2}=postmenopausal based on age ≥50 years; ^{3}=both.
§Relative risk.

development of breast cancer.[93,94] The evidence that a similar virus appeared in human breast milk has not been documented consistently.[94–97] Breastfeeding has undergone a dramatic secular trend in the United States, from a low frequency of breastfeeding in 29 percent of infants aged one week old in 1955[98] to a high proportion of breastfeeding in 67.5 percent of infants aged one week in 1998.[99,100] Birthweight of the neonate, ethnic-group, and socioeconomic status influence the proportion of infants who are breastfed and the duration of breastfeeding.[101] Since the 1960s, approximately 10 percent of infants are fed exclusively by soy formula, and breastfed infants may be supplemented with soy formula.[102]

Breastfeeding–Breast Cancer Association: Epidemiologic research, primarily designed as case-control studies, has demonstrated a modest, but not significant, lower risk of *premenopausal* breast cancer in those who reported having been breastfed[50,70,103–105] with two exceptions[106,107] (Table 5). Of the three studies in *postmenopausal* breast cancer, the R.Rs. vary above[106,107] and below the null value,[103] but none are significant. Having been breastfed is not associated with risk of breast cancer in women whose mothers later developed breast cancer.[103] In two studies, duration of breastfeeding is not associated with breast cancer risk.[50,107] Methodologic issues in this research area include: 1) inconsistent definition for breastfeeding across studies; 2) secular trends in birth weight and in breastfeeding, the latter of which is illustrated by birth year (Table 5), usually have not been taken into account; 3) maternal/daughter's recall of infant feeding postdiagnosis as a potential source of bias in all but one study;[107] 4) selection of controls who were born in the same era and at the same hospital as cases could reduce an association to the null,[105] because hospital policy is known to influence the opportunity to establish lactation.[108]

LINEAR GROWTH AND BODY SIZE FROM INFANCY THROUGH ADOLESCENCE

Rationale: Infancy and childhood are periods of rapid growth in weight, height, and brain size. Recent analyses of birth weight, childhood growth, and breast cancer risk have led to the exploration of factors influencing catch-up or -down growth in early childhood. In the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC), Ong[109] describes how thinner, shorter newborns with tall fathers experience the greatest catch-up in weight compared with those who show no change from birth to 2 years. Moreover, ALSPAC children with early catch-up growth have higher serum IGF-1 levels at 5 years than those remaining on trajectory or experiencing catch-down, after adjustment for current size.[110] A similar pattern of higher IGF-1 concentrations appear at 4 and 9 years of age in children who are thinner and smaller newborns, experience catch-up in linear growth, and have tall fathers.[111,112] Thus, in utero effects may be modulated by childhood growth velocity, genetic factors, and may correlate with IGF-1 concentrations in childhood.

Linear Growth/Body Fat–Breast Cancer Association: Linear growth velocity in 4 birth-(school)-cancer registry studies reveal an increased risk of breast cancer in girls who experience peak growth at 4–7 years,[113] 7 years,[114] up through 14 years of age,[44] or 12–18 years,[115] respectively (Table 6). In each study, high birth weight is associated with increased risk while high body mass at the respective ages is associated with reduced risk of breast cancer. In the Nurses' Health Study,[116] in a multiethnic retrospective cohort study from Hawaii,[117] a study in British Columbia,[118] in Norway,[119] and in Finland,[114] having more body fat at age 10 through adolescence is associated with a lower risk of breast cancer after adjustment for covariates. No such effect is observed in case-control studies with data on perception of height or body fat in childhood, puberty, or adolescence.[49,120,121]

In the 1946 British Birth Cohort study,[122] the median age at menarche is 7 months earlier in girls in the highest compared to the lowest three quartiles of height-for-age; and when age at menarche is added to the model of breast cancer risk, a significant interaction between birthweight and age at menarche appears (R.R.=2.2, 95%CI=1.1, 4.5) after adjustment for covariates. In the linked birth-school-cancer registry study in Finland, the hazard ratios for breast cancer are 1.2 (95%C.I.=1.1–1.4) for every kg/m^2 decrease in BMI at 7 years and 1.3 (95%CI=0.9–1.8) for every kg increase in birthweight.[114] In summary, being tall in prepubescent and pubescent periods is a risk factor for breast cancer[44,114,122] but does not appear as a risk factor until late pubescence and adolescence in the case-control study.[115] In contrast, being heavy throughout childhood and adolescence is associated with a lower risk of breast cancer.

Secular Trends in Puberty and Adolescence

Puberty begins approximately 3 years before menarche. Over the last century, the trends in earlier ages at onset of puberty and menarche are associated with longer lifetime exposures to hormones such as IGF-1 and estrogens.[123] African American girls have higher IGF-1 levels and experience puberty and menarche approximately 6 months earlier than non-Hispanic Whites (i.e., at 9 years, 64 percent of African American girls have started puberty in contrast with 33 percent of non-Hispanic Whites).[124] Compared to non-Hispanic White girls in the United States, African American and Hispanic girls have higher probabilities of reaching menarche by 11 years.[125] Later age at menarche is consistently associated with a reduced risk (with a range of 10 to 50 percent lower risk in breast cancer) in women who experienced menarche at $\geq$15 years versus $\leq$11 years.[116] Yet, a study of 245 African American families with breast cancer reported that a late age at menarche increases breast cancer risk in a putative breast cancer gene carrier and has a

TABLE 6
Growth patterns and relative risk of breast cancer by birth year, ethnic group, and menopausal status

Author[ref]	Birth year	Ethnic group	Cases†	Ages measurements were taken	R.R.	Comments
Cohort studies						
De Stavola[113]	1946	¥	51	2–4	0.9	Linear velocity (cm/year);
			53	4–7	1.3*	adjusted for age at
			49	7–11	1.0	menarche, age at first
			43	11–15	1.1	birth, parity and social class
			37	15–adulthood	0.9	
				7 yrs	Hazard ratio†	
Hilakivi-Clarke[114]	1924–1933	¥	22	≤114.5 cm	1.0 (ref)	P for trend in linear
			32	117.5	1.3	growth=0.01; adjusted
			39	120	1.7*	for birth weight and
			41	123	1.7*	birth length
			43	>123	1.9*	
				15 yrs		
		¥	23	≤153	1.0 (ref)	P for trend in linear
			34	157	1.3	growth=0.005; adjusted
			33	160	1.3	for birth weight and
			38	163	1.8*	birth length
			49	>163	1.9	
Case-control studies						
Herrinton[115]	1934–1963	¥, £	77	12–14	1.7*	Tall versus short height-at-age,
		¥, £	59	15–18	2.2*	controls matched on
						birth year, age at entry,
						marital status, alcohol use,
						race, parity, age at first
						birth and menopausal status
					R.R	
Ahlgren[44]	1930–1975	¥	3340	7–8 yrs	1.1*	Adjusted R.R. per
		¥		8–14 yrs	1.2*	5 cm increase;
						P for trend=0.01

£, African American.
¥, Non-Hispanic White.
#, Asian.
†Menopausal status: [0]=premenopausal; [1]=premenopausal based on age <50 years; [2]=postmenopausal based on age ≥50 years; [3]=both.
*95% confidence interval excludes one.

protective effect in a nongene carrier,[126] therefore interactions between gene polymorphisms and reproductive characteristics may be fine tune ethnic-group specific risk assessment. Recent secular trends in the 1990s reveal earlier ages at puberty and the adolescent growth spurt concurrent with a higher peak velocity in height, while age at menarche has stabilized.[127] In one cohort study, women who are in the 2 highest quintiles of linear growth velocity in adolescence have a 50 percent and 40 percent higher risk of *pre-* and *postmenopausal* breast cancer, respectively, compared to those in the lowest quintile.[116] In two case-control studies, the adjusted R.R.s of *premenopausal* (<46 years) and *postmenopausal* (50–64 years) breast cancer are reduced significantly in women who reach adult height at ≥18 years compared to women who reach final height at ≤13 years.[128,129] Finally a woman's adult height is a reflection of genetic factors, age at onset of ovarian function, and exposure to diet and to other environmental factors during adolescence. In a meta-analysis of several cohort studies, adult height is directly related to risk of *postmenopausal* breast cancer in non-Hispanic Whites but results are not as consistent for *premenopausal* breast cancer,[130] whereas the opposite pattern by menopausal status appeared in African American women.[131,132] Research from Norway,[119] the Netherlands,[133] and Finland[114] consistently

report a direct relation of adult height to breast cancer risk in women born during the Great Depression, who experienced puberty and adolescence during World War II.

METHODOLOGIC ISSUES

Life course research draws on data from prospective and retrospective studies in an effort to formulate a picture of the cumulative effects of exposures over developmental phases through the adult years. Hypotheses are explored from several vantage points. This effort requires an awareness of maternal and child health methodology and research, biologic plausability across disciplines ranging from reproductive physiology through carcinogenesis, and knowledge of secular trends that modify ''hypothesized'' associations.

Several essential methodologic issues in the analysis of anthropometric data such as birth weight or linear growth in childhood need to be addressed in future studies, and, if possible, could guide re-analysis of existing studies. Secular trends in guidelines for weight gain in pregnancy,[134] in rates of macrosomia,[38] and in rates of obesity vary by population and have implications for the underlying etiologic mechanisms related to in utero exposures and breast cancer risk. For example, since the 1960s, Dr. Eastman advocated higher weight gain in pregnancy in an effort to reduce the rates of low birth weight newborns in the United States. This action in tandem with the trend in obesity has been associated with higher rates of macrosomia in the United States, Canada, and other countries.[34] Thus, maternal weight gain in pregnancy is responsible for explaining a large percentage of the variation in birthweight-for-gestation.[32] Note, there are relatively recent guidelines for weight gain in pregnancy by prepregnancy BMI.

Research encompassing a range in birth cohorts that experienced life events such as the Great Depression, World War II, and the immediate postwar years requires stratified analysis of each era to address associations of birth parameters and childhood/pubertal growth with age at menarche and adult height. These birth cohort-specific analyses may reveal different interactions between birth anthropometrics, pubertal growth, and age at menarche with implications for breast cancer risk. For example, Robsahm[135] describes a 22 percent reduction in total caloric intake in Norway during WW II and reports women brought up in the ''non-food'' region have a lower risk of breast cancer than those in the ''food'' region.[136] Presentation of birth cohort specific growth patterns are illustrated[113] in the analysis of the 1946 British Birth Cohort. These data help to visualize growth patterns and their relation to cancer.

Infant and childhood anthropometric data typically are examined in light of an external referent growth curve derived from population-based studies, surveillance operations, or when external data are unavailable, an internal referent may be developed from the upper socioeconomic group of children in the respective study. Data are presented as Z-scores with recognized cut-offs for stunting and other high risk conditions by the World Health Organization. Z-scores enable comparisons across studies. To date, the results of anthropometric data in infancy and childhood have been presented in a mixed fashion; some use referent data[114,122] while others do not.[41,115]

A search for one category of birthweight (e.g., low or high birthweight) as ''the'' risk group might not be fruitful, since many endpoints do not reflect true thresholds. Consider, for example, one-third of all infant deaths in the United States occur to newborns of normal to high birthweight—a misunderstood phenomenon reflected in the graded decline in infant mortality with increasing birth weight (in 500 g increments) until a slight increase in newborns weighing $\geq$4,500 grams.[137] Moreover, ethnic group-specific birthweight distributions differ as do the birthweight-specific infant mortality rates. A description of the distribution of birthweight and birth length, as well as the percentage of SGA and LGA, in research studies may provide clues why certain ethnic groups do or do not have a LGA-breast cancer association. Also, an analysis that takes into account gestational age might clarify whether birth size or fetal growth velocity is of import, or preterm births of LGA are at risk of breast cancer. Finally, birth length and other anthropometrics such as leg length can be riddled with measurement error and require routinized standardization of techniques and tools. To date, inadequate information about the procedures for anthropometric data collection, training, and reproducability have been provided across studies. In short, anthropometric data in infancy and childhood need to be seriously examined for sources of measurement error prior to addressing the biological implications of the findings.[138]

The assessment of an association between breastfeeding and breast cancer is marred by inadequate questionnaire-based data on the duration of exclusive from partial breastfeeding and on the timing and type of infant feeding supplements. A core set of infant feeding questions for exposure assessment across studies should consider tools like calendar-based historical records to enhance recall and use of sources such as baby books to assess reporting bias. Infant feeding choice at birth covaries by birthweight; analysis needs to examine the relation within birthweight categories.[101]

CONCLUSION

Although more than 20 studies of birthweight, birth length, and preterm births have been published, there is no consistent association between a birth parameter and breast cancer risk (Table 7). The strongest effects on breast cancer can be seen in birth length (albeit research is limited) and linear growth velocity from childhood through adolescence, for which the most consistent associations appear. The biological implications for breast cancer of linear growth velocity in childhood and adolescence require an understanding of hormonal-immunologic contributors and their genetic variants within birthweight-for-gestational-age groups. Such research may

TABLE 7
Summary of literature on early-life exposures and breast cancer

Exposure	No. studies with significant findings*/ total no. studies	Range R.R.
High birth weight		
Premenopausal	3/7	3.1–5.0
Postmenopausal	0/3	—
Both	5/11	1.2–2.6
Birth Length	2/4	1.5–3.5
Preterm	3/8	2.1–6.7
Preeclampsia	6/9	0.3–1.4
Maternal age	2/12	1.5–2.0
Infant feeding	0/7	0.7–1.3
Linear growth	4/4	1.1[a]–1.9

*95% confidence interval excludes one.
[a]Adjusted R.R. per 5 cm increase.

best be conducted in nonhuman primates who are hormonally similar to humans. Further work needs to be done on the effects of secular trends and life events on growth patterns in childhood and adolescence, which has not been adequately examined by birth cohort except in two studies.[113,114] Critical gaps in research exist without additional work on ethnic groups other than non-Hispanic Whites/Europeans. We seek to investigate early-life exposures and breast cancer risk, yet we have not acknowledged that pregnancy is a controlled metastatic state with upregulation of genes such as twist, involved in neurologic development in embryogenesis, and reappear involved in metastasis of mammary tumors.[139] Perhaps we have been short-sighted in our failure to recognize how cancer mirrors elements of reproductive physiology.

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